General

Guideline Title

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb 24. 22 p. (Technology appraisal guidance; no. 385).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Nov. 30 p. (Technology appraisal guidance; no. 132).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

This guidance should be used with the National Guideline Clearinghouse (NGC) summary of the National Institute for Health and Care Excellence (NICE)'s guideline Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease and the NICE clinical guideline Familial hypercholesterolaemia: identification and management .

Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated.

Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who cannot tolerate statin therapy (as defined below).

Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who have started statin therapy when:

- Serum total or low-density lipoprotein cholesterol (LDL-c) concentration is not appropriately controlled (as defined below) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined

below) and
- A change from initial statin therapy to an alternative statin is being considered

When prescribing ezetimibe co-administered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

For the purposes of this guidance, intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.

For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease in the relevant populations.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Primary heterozygous-familial or non-familial hypercholesterolaemia

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of ezetimibe as monotherapy or combination therapy for treating primary heterozygous-familial and non-familial hypercholesterolaemia

Target Population

Adults (18 years of age and older) with primary heterozygous-familial or non-familial hypercholesterolaemia

Interventions and Practices Considered

1. Ezetimibe monotherapy
2. Ezetimibe coadministered with statin therapy

Major Outcomes Considered

- Clinical effectiveness
  - Low-density lipoprotein-cholesterol (LDL-c) (mean % change from baseline)
  - Total cholesterol (TC) reduction (mean % change from baseline)
  - Apolipoprotein B
  - Lipoprotein (a)
  - Adverse events (AEs and serious AEs)
  - Cardiovascular (CV) events
  - Health-related quality of life
  - Survival/mortality
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Aberdeen Health Technology Assessment (HTA) Group (see the Committee Papers in the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches

The company submission provides full details of the searches that were undertaken to identify the included studies for the clinical effectiveness review. The major relevant databases: MEDLINE (Ovid), EMBASE (Ovid) and CENTRAL (Cochrane Library) were searched on 9th March 2015 for publications written in English and published from 1990 onwards. Conference proceedings were not searched separately. However, EMBASE includes abstracts published in journals, so the contents of major conferences are likely to have been included.

The search strategies are documented in full in Appendix 4 of the ERG report and are reproducible. The MEDLINE and EMBASE strategies appropriately combined four search facets using the Boolean operator AND: hypercholesterolaemia; ezetimibe; statin or placebo; and randomised controlled trial (RCT). The search in the Cochrane Library for CENTRAL excluded the RCT facet, which was appropriate. Although both thesaurus terms (MeSH or Emtree) and free text terms were used, the ERG does not consider that the search was as sensitive as it should have been (particularly for MEDLINE) and therefore cannot confirm that the company's approach was comprehensive in identifying relevant studies. The hypercholesterolaemia facet of the search was of particular concern:

- *Hypercholesterolaemia* is not the correct MeSH or Emtree term. While Emtree automatically maps to the correct term *Hypercholesterolemia*, MEDLINE and the Cochrane Library return no hits because this term is invalid.

- The MeSH term for familial hypercholesterolaemia (*Hyperlipoproteinemia Type II*) has not been included in the MEDLINE and Cochrane Library searches.
- The sensitivity of the search could have benefited by the inclusion of thesaurus and text terms related to the associated concepts of *hyperlipidaemia* and *dyslipidaemia*.

See the ERG report for additional information about other issues of concern.

The ERG notes that there is a discrepancy in the number of hits obtained before removal of the duplicates in the flow diagram (N=1775) as compared to the total number of hits obtained by the searches as detailed in Appendix 4 (N=414+1044+362=1820). This difference may be due to restricting the searches to publications published after 1990, which has not been reported in Appendix 4. The company submission states that no relevant ongoing studies were identified but no information was given as to what searching was undertaken to establish this.

Inclusion Criteria

The company's systematic review of effectiveness involves two discrete comparisons: ezetimibe monotherapy versus placebo and ezetimibe in combination with a statin versus statin alone. There are, therefore, two distinct sets of inclusion criteria applied in the company's systematic review of clinical evidence.

Inclusion Criteria Used in the Systematic Review of Clinical Effectiveness: Ezetimibe Monotherapy

Clinical Effectiveness	Inclusion Criteria	Exclusion Criteria
Population	Adults >18 years with primary hypercholesterolaemia	• Adults with homozygous familial hypercholesterolaemia • Adults with homozygous sitosterolaemia • Secondary hypercholesterolaemia • Paediatric populations
Intervention	Ezetimibe 10 mg (ezetimibe, ezetrol, zetia, vytorin, inegy)	Other lipid modifying therapy (nicotinic acid, bile acid sequestrants, fibrates, omega-3 fatty acids)
Comparators	Placebo	
Outcomes	• Low-density lipoprotein cholesterol (LDL-c) reduction (mean % change from baseline) • Total cholesterol (TC) reduction (mean % change from baseline) • Apolipoprotein B • Lipoprotein (a) • Adverse events (AEs and serious AEs)	
Study design	Randomised controlled trials (RCTs) >12 weeks	Non-RCTs
Language restrictions	English	
Other	Studies from 1990 onwards	

Inclusion Criteria Used in the Systematic Review of Clinical Effectiveness: Ezetimibe in Combination with a Statin

Clinical Effectiveness	Inclusion Criteria	Exclusion Criteria
Population	Adults >18 years with primary hypercholesterolaemia	• Adults with homozygous familial hypercholesterolaemia • Adults with homozygous sitosterolaemia • Secondary hypercholesterolaemia • Paediatric populations
Intervention	• Ezetimibe 10 mg + atorvastatin 10-80 mg • Ezetimibe 10 mg + simvastatin 10-80 mg • Ezetimibe 10 mg + pravastatin 10-40 mg • Ezetimibe 10 mg + fluvastatin 20-80 mg	Other lipid modifying therapy (nicotinic acid, bile acid sequestrants, fibrates, omega-3 fatty acids)

Clinical Effectiveness	Inclusion Criteria	Exclusion Criteria
Comparators	• Ezetimibe 10 mg + rosuvastatin 5-40 mg Matching statin dose: • Atorvastatin 10-80 mg • Simvastatin 10-80 mg • Pravastatin 10-40 mg • Fluvastatin 20-80 mg • Rosuvastatin 5-40 mg	
Outcomes	• Low-density lipoprotein cholesterol (LDL-c) reduction (mean % change from baseline) • Total cholesterol (TC) reduction (mean % change from baseline) • Apolipoprotein B • Lipoprotein (a) • Adverse events (AEs and serious AEs)	
Study design	randomised controlled trials (RCTs) >12 weeks	Non-RCTs
Language restrictions	English	
Other	Studies from 1990 onwards	

The company's inclusion criteria for the ezetimibe monotherapy population specify the intervention as "ezetimibe 10 mg (ezetimibe, ezetrol, zetia, vytorin, inegy)". However, both vytorin and inegy should be regarded as combination therapy rather than monotherapy since, according to the Summary of Product Characteristics (SmPC), they contain 10 mg ezetimibe and 20 mg simvastatin. The ERG assumes that inegy and vytorin have been included in the company's submission by mistake.

The inclusion criteria did not refer to various other outcomes listed by the company, such as survival, cardiovascular events, stroke and health-related quality of life. At clarification, the company confirmed that CV events and survival/mortality were eligible for inclusion in the systematic review of clinical effectiveness.

Within the eligibility criteria used for the systematic review of clinical evidence the company indicates "RCTs >12 weeks", which, in theory, would preclude inclusion of trials of 12 weeks duration. However, in the text of the submission they state that "RCTs with a treatment period of 12 weeks or greater were included". Considering that a number of studies included in the systematic review of clinical evidence were of 12 weeks duration, the ERG assumes that the text of the submission reflects the correct approach.

Cost-effectiveness

ERG Comment on Company's Review of Cost-effectiveness Evidence

State Objectives of Cost-effectiveness Review. Provide Description of Company's Search Strategy and Comment on Whether the Search Strategy Was Appropriate

The manufacturer updated the systematic review of economic evaluations that was conducted for NICE Technology Appraisal 132 (TA132). MEDLINE (Ovid), EMBASE (Ovid), National Health Service Economics Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) Database (both the Centre for Reviews and Dissemination [CRD] and Cochrane Library interfaces) were searched on 4th March 2015 for publications in English from 2006 onwards to identify studies published since TA132. In addition recent relevant conference proceedings from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), European Atherosclerosis Society (EAS), American College of Cardiology (ACC) and European Society of Cardiology (ESC) were searched from 2013.

The searches are documented in full in the manufacturer's submission and are fully reproducible. The MEDLINE and EMBASE search strategies included both thesaurus terms (MeSH or EMTREE) and free text terms and combined the concepts of hypercholesterolaemia and cost-effectiveness while for NHS EED and the HTA database only the concept of hypercholesterolaemia was included.

The inclusion of additional terms would have been beneficial. As was the case with the clinical effectiveness searches, the sensitivity of the hypercholesterolaemia facet could have been enhanced by the inclusion of related terms such as hyperlipidaemia and dyslipidaemia and associated conditions, particularly cardiovascular and coronary diseases. However, unlike the clinical effectiveness searches, the correct MeSH and Emtree terms for hypercholesterolaemia were used.

For the cost-effectiveness facet the inclusion of the following could have been beneficial:

- MeSH term *Exp "costs and cost analysis"*
- Emtree term *Exp economic evaluation/*
- MeSH *Technology Assessment, Biomedical/* and Emtree *Biomedical technology assessment/*

There was inconsistency whereby the MEDLINE search did not use terms relating to Monte Carlo methods and Markov models while the EMBASE search did.

Key conference abstracts for 2013-5 were searched and employed a keyword search to identify relevant studies. Keywords used related to the clinical condition and included hypercholesterolemia as well as stroke, myocardial infarction and angina.

State the Inclusion/Exclusion Criteria Used in the Study Selection and Comment on Whether They Were Appropriate

The scope of the review was defined in terms of population (adults age 18 or older with primary hypercholesterolaemia), intervention/comparator (ezetimibe, statins, other lipid lowering drugs), outcomes (inputs and outcomes reported in economic evaluations) and study design (cost-effectiveness analyses and cost-utility analyses). Models that assessed the cost-effectiveness of ezetimibe and or other lipid lowering drugs versus an appropriate comparator were included. Restrictions were made to include only studies conducted for UK populations and those published in English language. These restrictions appear appropriate for identifying studies to inform the specific question of whether ezetimibe offers a cost-effective option from the UK NHS perspective. However, some of the exclusion criteria may have ruled out studies potentially relevant for informing model structure.

What Studies Were Included in the Cost-effectiveness Review and What Were Excluded? Where Appropriate, Provide a Table of Identified Studies. Please Identify the Most Important Cost-effectiveness Studies

Seven full cost-effectiveness and cost-utility analyses were identified in line with the original scope of the review, and a further two cost-effectiveness models were deemed relevant because they described model structures and inputs that were utilised by included economic studies. It was stated that these two studies originally fell outside the scope of the review because they did not focus specifically on patients with hypercholesterolaemia or ezetimibe as a primary intervention. However, a number of the seven originally included studies also did not include ezetimibe as an intervention or comparator, and so it is not entirely clear why the two additional models were deemed to be outside the original scope. The table of included studies presented in the company's submission is reproduced in Table 11 of the ERG report.

Number of Source Documents

Clinical Effectiveness

- Thirty publications were included in qualitative synthesis.
- Twenty-seven studies were included in quantitative synthesis.

See Figure 5 in the manufacturer's submission (see the Committee Papers in the "Availability of Companion Documents" field) for the flow diagram of included and excluded publications.

Cost-effectiveness

- Nine cost-effectiveness and cost-utility analyses were included.
- The manufacturer submitted an economic evaluation.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Aberdeen Health Technology Assessment (HTA) Group (see the Committee Papers in the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Critique of Data Extraction

The company followed the general principles recommended by the University of York Centre for Reviews and Dissemination (CRD) to assess current evidence. The ERG considers the methods described in this publication to be appropriate. Title/abstract screening and full text screening were carried out by two independent reviewers, with any disagreements resolved by discussion. The data extraction process used by the company and the number of reviewers involved are not detailed in the submission as well as the number of reviewers involved in the quality assessment of the selected studies.

Quality Assessment

Risk of bias of included studies was based on an adaptation of the criteria specified in the CRD guidelines. The criteria involved assessment of selection bias, performance bias, detection bias, attrition bias and reporting bias and this is considered appropriate by the ERG.

According to the company's assessment of risk of bias, the majority of trials included in the systematic review of clinical evidence were conducted with appropriate randomisation and concealment of allocation methods, blinding procedures, balance of groups at baseline, and treatment of missing data and analyses.

The ERG conducted a broad assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria. Results are presented in Table 8 of the ERG report.

Critique of Trials of the Technology of Interest, Their Analysis and Interpretation (and Any Standard Meta-analyses of These)

All trials included ezetimibe with a dose of 10 mg, but statin doses varied in the included trials and some studies included multiple arms comparing various doses of statin such as 10, 20, 40 and 80 mg.

Meta-analyses have been conducted for two comparisons:

- Ezetimibe 10 mg monotherapy versus placebo
- Ezetimibe 10 mg plus statin versus matching statin dose

The following outcomes have been assessed:

- Percentage change from baseline in low-density lipoprotein cholesterol (LDL-c)
- Percentage change from baseline in total cholesterol (TC)

Data for two additional outcomes, apolipoprotein B and lipoprotein (a), were also extracted and appear in Appendix 10 of the company's submission. Meta-analyses have not been conducted for these outcomes. No explicit reason for this choice is provided in the submission, although it appears from Appendix 10 that data were not always available and, in particular, standard deviations were often missing.

The pooled results from the four main conducted meta-analyses are shown in Table 9 of the ERG report. In each case a random effects model was used and meta-analyses were based on mean differences in percentage change scores. The results show evidence of benefits in favour of greater

lowering of LDL-c and TC for ezetimibe versus placebo and for ezetimibe plus statin versus matching statin dose.

Each of these meta-analyses showed high levels of statistical heterogeneity (I^2>99%). This means that there were very high levels of inconsistency between the trials included in the meta-analyses (95% confidence intervals for different trials rarely overlap).

For the percentage change in LDL-c and TC for ezetimibe plus statin versus matching statin dose three meta-analyses have been presented with studies split into subgroups: first by the type of statin, second by the dose of statin (for simvastatin studies only) and third by diabetes status (for studies reporting diabetic and non-diabetic subgroups). At clarification, the results by type of statin were updated to reflect the errors in the original submission. Broadly consistent results were shown in each of these subgroup analyses.

See Section 4 of the ERG report for additional critique of the methods of review.

Cost-effectiveness

What Does the Review Conclude from the Data Available? Does the ERG Agree with the Conclusions of the Cost-effectiveness Review?

The included studies were each summarised narratively, tabulated for comparison and quality appraised using the Drummond checklist (see Appendix 15 of company's submission). No overarching conclusion was drawn regarding the cost-effectiveness of ezetimibe as a monotherapy or as an add-on to statin therapy based on the reviewed studies. Rather, the key objective of the review (although not specially stated) appears to have been to identify appropriate modelling frameworks for addressing the current decision problem.

Refer to Section 5.1.4 in the Assessment Report for additional information.

Summary and Critique of Company's Submitted Economic Evaluation by the ERG Suggested Research Priorities

Models Structure

vo Markov model with annual cycle was developed by the company. A copy of the model schematic provided in their submission is reproduced in Figure 2 of the ERG report. The model simulates the occurrence of cardiovascular (CV) events for both primary and secondary prevention cohorts. Modelled CV events include those included in datasets used to derive the Q-Risk prediction algorithm, i.e., stable angina (SA), unstable angina (UA), myocardial infarction (MI), stroke, transient ischaemic attack (TIA) and CV death. SA and TIA are excluded from the company's base case analysis due to a lack of direct evidence demonstrating the effects of statins on these events, or evidence linking the effects of LDL-c reduction to relative reductions in the incidence of these events. There is an option to include SA and TIA in scenario analysis, with treatment effects modelled to be equivalent to those observed for MI (SA) and stroke (TIA). Note, however, that the omission of risks for SA and TIA will have knock-effects on the risk of subsequent events and CV mortality. Thus it seems inappropriate to exclude any risk of these events from the model in the base case analysis. If it is considered appropriate not to model any effects of ezetimibe and/or statins on these events, then the relevant treatment effects should be switched off in the model, and not the baseline risks of these events. This latter specification was however included as a scenario analysis by the company.

For the primary prevention analyses, the cohort commences in a "well" state, and can experience events as determined by the estimated baseline transition probabilities for first CV events. Each CV event is modelled using two states, reflecting costs and utilities incurred within the first year of the event and then longer-term costs and utilities incurred in subsequent years (post-event health states). For the secondary prevention analyses, the cohort is initially distributed across the post-UA, post-MI and post-stroke states, and can experience any of these events in subsequent cycles of the model based on estimated transition matrices for secondary CV events.

Treatment effects for statins and ezetimibe are incorporated as relative risks or rate ratios for non-fatal MI, unstable angina, stroke, any vascular death and non-vascular deaths. The relative risks for statin treatment are taken directly from a previous meta-analysis conducted for NICE clinical guideline 181 (CG181) which estimated the direct effects of statin therapy on CV endpoints (MI, stroke, CV death). Since unstable angina was not included as an outcome in the meta-analysis for CG181, the associated relative risk for unstable angina is assumed to be equal to that observed for MI. The rate ratios associated with ezetimibe use are derived indirectly through an estimated relationship between LDL-c reductions and relative reductions in the risk of the defined CV events. The Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of 26 statin trials provides estimated rate ratios per 1 mmol/L reduction in LDL-c for MI, stroke, any vascular death and non-vascular death. Thus modelled reductions in LDL-c associated with ezetimibe use (as monotherapy or add-on to statin), were linked to reductions in CV events through these estimated relationships. Again, the rate ratio for MI was also assumed to apply for the effects of ezetimibe on unstable angina.

See Section 5 of the ERG report for more information on the cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an Assessment Report. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the Appraisal Consultation Document (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the Final Appraisal Determination (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence. Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee decided that the company's cost-effectiveness estimates according to primary and secondary prevention of cardiovascular disease using IMPROVE-IT were not suitable for decision-making.

How Has the New Cost-effectiveness Evidence That Has Emerged Since the Original Appraisal (TA132) Influenced the Current Recommendations?

The Committee considered the incremental cost-effectiveness ratios (ICERs) from the original appraisal of ezetimibe to be more plausible than the current estimates from the company and Evidence Review Group (ERG) because the population in the original appraisal was better aligned with

the final National Institute for Health and Care Excellence (NICE) scope, current practice and ezetimibe's marketing authorisation.

It decided not to use the company and ERG's current cost-effectiveness estimates for ezetimibe for its decision-making. It further concluded that the recommendations in NICE's original technology appraisal guidance on ezetimibe were still appropriate. The Committee agreed to amend the recommendations so that they no longer referred to superseded NICE guidance.

Patient Access Schemes (Pharmaceutical Price Regulation Scheme [PPRS])

The Committee concluded that the PPRS payment mechanism was not relevant in considering the cost-effectiveness of ezetimibe.

See Sections 3 and 4 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination (FAD).

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of ezetimibe and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from randomised controlled trials (RCTs). For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Ezetimibe is a cholesterol-absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols, without affecting the uptake of triglycerides or fat-soluble vitamins.
- The evidence demonstrates that ezetimibe provides a valuable treatment option for patients that require cholesterol lowering in order to reduce their risk of developing cardiovascular disease (CVD) or a cardiovascular-related event.

Potential Harms

Adverse reactions with ezetimibe as monotherapy or with a statin are usually mild and transient. When given as monotherapy, they most commonly include abdominal pain, diarrhoea, flatulence and fatigue. When taken with a statin, the most common additional adverse reactions include

increased alanine transaminase, aspartate transaminase or both, headache and myalgia.

For full details of adverse effects and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse effects and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- The recommendations in this guidance represent the view of the National Institute for Health and Care Excellence (NICE), arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.
- Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the National Health Service (NHS) Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has primary heterozygous-familial or non-familial hypercholesterolaemia and the doctor responsible for their care thinks that ezetimibe is the right treatment, it should be available for use, in line with NICE's recommendations.

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb 24. 22 p. (Technology appraisal guidance; no. 385).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Feb 24

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Andrew Stevens (*Chair of Appraisal Committee C*), Professor of Public Health, University of Birmingham; Professor Eugene Milne (*Vice Chair of Appraisal Committee C*), Director of Public Health, City of Newcastle upon Tyne; Professor Kathryn Abel, Institute of Brain and Behaviour Mental Health, University of Manchester; Mr David Chandler, Lay Member; Mrs Gail Coster, Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust; Professor Peter Crome, Honorary Professor, Department of Primary Care and Population Health, University College London; Professor Rachel A Elliott, Lord Trent Professor of Medicines and Health, University of Nottingham; Dr Nigel Langford, Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary; Dr Andrea Manca, Health Economist and Senior Research Fellow, University of York; Dr Patrick McKiernan, Consultant Pediatrician, Birmingham Children's Hospital; Dr Iain Miller, Founder and Chief Executive Officer, Health Strategies Group; Professor Stephen O'Brien, Professor of Haematology, Newcastle University; Dr Anna O'Neill, Deputy Head of Nursing and Health Care School/Senior Clinical University Teacher, University of Glasgow; Professor Peter Selby, Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust; Professor Matt Stevenson, Technical Director, School of Health and Related Research, University of Sheffield; Dr Paul Tappenden, Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield; Professor Robert Walton, Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry; Dr Judith Wardle, Lay Member

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. London (UK): National Institute for Health and Clinical Excellence (NICE); 2007 Nov. 30 p. (Technology appraisal guidance; no. 132).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. Resource impact report. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb. 3 p. (Technology appraisal guidance; no. 385). Available from the NICE Web site .
- Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. Committee papers. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Sep. 520 p. Available from the NICE Web site .

Patient Resources

The following is available:

- Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb. 3 p. (Technology appraisal guidance; no. 385). Available from the NICE Web site . Also available for download in ePub and eBook formats from the NICE Web site . Also available in Welsh from the NICE Web site .

NGC Status

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